Abacavir sulfate

Brand Name: Ziagen

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Drug Description

Abacavir is a synthetic analogue of guanine, a naturally occurring purine nucleoside. It differs structurally from other reverse transcriptase inhibitors (didanosine, lamivudine, stavudine, zalcitabine, and zidovudine) in that it is a carbocyclic nucleoside analogue rather than a dideoxynucleoside analogue. [1]

HIV/AIDS-Related Uses

Abacavir sulfate was approved by the FDA on December 17, 1998, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children.[2] In initial clinical studies, abacavir was used in combination with two other nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine). Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to loss of virologic response.[3]

Abacavir is used in conjunction with other antiretroviral agents for postexposure prophylaxis of HIV infection in health care workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with blood, tissues, or other body fluids associated with a risk for HIV transmission.[4]

Pharmacology

Abacavir is a carbocyclic nucleoside analogue. It is converted by cellular enzymes to the active metabolite, carbovir triphosphate. An analogue of deoxyguanosine-5'-triphosphate (dGTP), carbovir triphosphate inhibits HIV-1 reverse transcriptase (RT) by competing with the natural substrate dGTP for incorporation into viral DNA. Once incorporated, carbovir triphosphate causes premature termination of viral DNA synthesis. In vitro, abacavir had synergistic activity in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine.[5] Abacavir is a weak inhibitor of cellular DNA polymerases alpha, beta, and gamma.[6]

Abacavir sulfate is well absorbed following oral administration, with a bioavailability of approximately 83%. After oral administration of 300 mg twice daily, the mean steady-state peak serum abacavir concentration (Cmax) was 3.0 +/- 0.89 mcg/ml, and the 0- to 12-hour area under the concentration-time curve (AUC) was 6.02 +/- 1.73 mcg·hr/ml. Systemic absorption is comparable following administration of tablets and oral solution.[7]

Following intravenous administration of abacavir sulfate, the apparent volume of distribution is 0.86 L/kg, suggesting distribution into extravascular spaces. Abacavir is distributed into cerebrospinal fluid (CSF). The steady-state CSF to plasma AUC ranges from 27% to 33%. Abacavir also readily distributes into erythrocytes. Plasma protein binding is approximately 50% and is independent of drug concentration.[8]

Abacavir is metabolized in the liver by alcohol dehydrogenase and glucuronyl transferase to form the metabolites 5'-carboxylic acid and 5'-glucuronide, neither of which have antiviral activity. Involvement of cytochrome P450 isoenzymes in metabolizing abacavir is limited. Following oral administration of a 600 mg dose of radiolabeled abacavir, 82.2% of the dose is excreted in urine and 16% is excreted as feces, with unchanged abacavir accounting for 1.2% of recovered radioactivity in urine. The elimination half-life following a single dose is approximately 1.5 hours.[9]

Abacavir sulfate is in FDA Pregnancy Category C.[10] No adequate or well-controlled studies of abacavir have been done in pregnant women. Studies in laboratory animals have shown that abacavir crosses the placenta, with evidence of fetal toxicity at dosage levels many times higher than the corresponding dose for humans. Abacavir should be used in pregnancy only if the potential benefits outweigh the risks. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to abacavir

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Pharmacology (cont.)

and other antiretrovirals. Physicians may register patients by calling (800) 258-4263 or at http://www.APRegistry.com. It is not known whether abacavir is excreted in human milk; it is excreted in the milk of laboratory animals. Because of the potential for HIV transmission and for serious adverse effects from abacavir to the breast-fed infant, women should be instructed not to breast-feed while taking abacavir.[11]

HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the RT gene resulting in amino acid substitutions. Phenotypic analysis of HIV-1 isolates that harbored abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a threefold decrease in susceptibility to abacavir in vitro.[12]

Recombinant laboratory strains of HIV-1 (HXB2) containing multiple RT abacavir-resistance mutations exhibited cross resistance to lamivudine, didanosine, and zalcitabine in vitro. In clinical trials, patients who had previous prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs) or who had HIV-1 isolates containing multiple mutations that conferred resistance to NRTIs had limited response to abacavir. The potential for cross resistance between abacavir and other NRTIs should be considered in the choice of therapeutic regimens in therapy-experienced patients.(8) An increasing number of thymidine analogue mutations (TAMs) is associated with a progressive reduction in abacavir susceptibility.[13]

Cross resistance between abacavir and protease inhibitors (PIs) is unlikely because the drugs target different enzymes; cross resistance between abacavir and nonnucleoside reverse transcriptase inhibitors (NNRTIs) also is unlikely due to different binding sites and mechanisms of action.[14]

Adverse Events/Toxicity

Fatal hypersensitivity reactions have been associated with abacavir therapy. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, or cough) should discontinue abacavir as soon as a hypersensitivity reaction is suspected. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications). Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of abacavir in patients who have no identified history of unrecognized symptoms of hypersensitivity to abacavir therapy. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.[15]

In clinical studies, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric patients receiving abacavir in conjunction with lamivudine and zidovudine. Hypersensitivity-related fatalities have also been reported with abacavir use. Hypersensitivity reactions are characterized by symptoms indicating involvement of multiple organ and body systems and usually appear within the first 6 weeks of abacavir therapy, although they may appear at any time.[16] Signs and symptoms of hypersensitivity include skin rash or a combination of two or more of the following: fever; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, and cough.[17] Other signs and symptoms include malaise, lethargy, myalgia, myolysis, headache, arthralgia, edema, paresthesia, lymphadenopathy, and mucous membrane lesions such as conjunctivitis and mouth ulcerations. Laboratory abnormalities indicating hypersensitivity reaction include lymphopenia and

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Adverse Events/Toxicity (cont.)

increases in serum concentrations of liver enzymes, creatine kinase, or creatinine. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions.[18]

Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals.[19] These conditions are sometimes fatal. The majority of cases have occurred in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised in any patient with known risk factors for liver disease; however, cases have been reported in patients with no known risk factors. Treatment with abacavir sulfate should be suspended in any patient who develops clinical or laboratory findings that suggest lactic acidosis or pronounced hepatotoxicity.[20]

Among the most frequently reported side effects of abacavir are many of the signs and symptoms of hypersensitivity reaction, including nausea and/or vomiting, diarrhea, fever, chills, and malaise or fatigue. These symptoms have been reported in up to 60% of patients, but clinical trial results show that only about 5% of adult and pediatric patients experience abacavir hypersensitivity. Nevertheless, if hypersensitivity is suspected, patients should stop taking abacavir and seek immediate medical evaluation. Other frequently reported adverse effects include headache, insomnia, and loss of appetite. In one study, some pediatric patients experienced nausea and vomiting, diarrhea, loss of appetite, and skin rashes. In another study, some patients reported worsening of pre-existing depression. Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were observed in patients receiving abacavir in combination with medications known to be associated with SJS and TEN. Erythema multiforme has also been reported. Redistribution of body fat, hyperglycemia, lipid metabolism disorders, pancreatitis, and elevated gamma glutamyl transferase (GGT) have also been associated with abacavir use.[21]

In clinical trials performed in treatment-naive adults given abacavir with lamivudine/zidovudine, the most common adverse effects observed were nausea, headache, malaise and fatigue, and vomiting.[22] In a study of treatment-experienced pediatric patients who received abacavir, lamivudine, and zidovudine twice daily, laboratory abnormalities (e.g., anemia, neutropenia, liver function test abnormalities, CPK elevations) were observed with similar frequencies as in a study of treatment-naive adults who received abacavir and lamivudine twice daily with efavirenz once daily.[23]

Drug and Food Interactions

Abacavir may be taken with or without food. Administering the drug with food did not significantly decrease abacavir AUC as compared with administration during the fasting state.[24] Alcohol ingested during treatment with abacavir may result in increased concentrations and half-life of abacavir due to competition for common metabolic pathways. One study showed that abacavir does not affect blood ethanol concentrations, but ethanol does increase exposure to abacavir. This increase is not considered clinically significant because the abacavir AUC is well within the acceptable range seen in previous studies.[25]

In human liver microsomes, abacavir did not significantly inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4); therefore, clinically important interactions between abacavir and drugs metabolized through these pathways are not expected.[26] [27]

Coadministration of abacavir and the PI amprenavir increases bioavailability and plasma concentrations of amprenavir but does not require dosage adjustment, according to the amprenavir manufacturer. Results of in vitro studies using some HIV PIs indicate that the antiretroviral effects of these drugs and abacavir are synergistic against HIV-1.[28]

Although clinically significant pharmacokinetic interactions have not been observed in patients taking abacavir together with the NRTIs lamivudine and zidovudine, the antiretroviral effects of abacavir combined with the NRTIs

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Drug and Food Interactions (cont.)

didanosine, lamivudine, stavudine, or zalcitabine are additive or synergistic against HIV-1 in vitro. Clinically important interactions with the NNRTIs delavirdine, efavirenz, and nevirapine are not expected. In vitro studies have demonstrated synergistic activity between abacavir and nevirapine.[29]

Concomitant use of abacavir with methadone may increase clearance of methadone but does not affect the pharmacokinetics of abacavir. In a study of HIV infected patients receiving methadone-maintenance therapy with concomitant high-dose abacavir therapy, clearance of oral methadone increased by 22%. The manufacturer of abacavir states that this alteration will not require dosage modification of methadone in most patients; however, an increased methadone dosage may be necessary in a small number of patients.[30] [31]

Contraindications

Abacavir has been associated with fatal hypersensitivity reactions and should not be restarted following a hypersensitivity reaction to abacavir. Abacavir is contraindicated in patients with previously demonstrated hypersensitivity to abacavir sulfate or any of the components of the products.[32] A Medication Guide and Warning Card summarizing the symptoms of abacavir hypersensitivity reactions should be dispensed by the pharmacist with each new prescription and refill of abacavir (or an abacavir-containing product such as Trizivir). Patients being treated with abacavir should carry the Warning Card with them.[33]

Clinical Trials

For information on clinical trials that involve Abacavir sulfate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Abacavir sulfate AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[34]

Dosage Form: Film-coated tablets containing 300 mg of abacavir; oral solution containing 20 mg/ml of abacavir. The recommended dose of abacavir for adults is 300 mg twice daily in combination with other antiretroviral agents. The recommended dose of abacavir for adolescents and pediatric patients age 3 months to 16 years is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents. The recommended dose of abacavir in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, abacavir oral solution (10 ml twice daily) should be used for the treatment of these patients.[35]

Storage: Tablets and oral solution should be stored at controlled room temperature of 20 C to 25 C (68 F to 77 F). Oral solution may be refrigerated but should not be frozen.[36]

Chemistry

CAS Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (1:1)[37]

CAS Number: 188062-50-2[38]

Molecular formula: (C14-H18-N6-O)2-H2SO4[39]

C50.1%, H5.7%, N25.1%, O14.3%, S4.8%[40]

Molecular weight: 670.76[41]

Physical Description: Abacavir sulfate is a white to off-white solid. Oral solution is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.[42]

Solubility: 77 mg/ml in distilled water at 25 C.[43]

Other Names

ABC sulfate[44]

ABC[45]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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